Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Potassium Dimethyldithiocarbamate

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Office of Environmental Health Hazard Assessment (OEHHA)
Reproductive and Cancer Hazard Assessment Section

Summary

The maximum allowable dose level (MADL) for potassium dimethyldithiocarbamate exposure is **720 micrograms/day (µg/day)**. The MADL values were derived as described below, based on a developmental toxicology study in rabbits (Rodwell, 1988b).

Background

This report describes the derivation of a MADL for potassium dimethyldithiocarbamate (CAS No. 128-03-0).

Potassium dimethyldithiocarbamate is currently registered as a pesticide in California. The range of use in California over the last 10 years (1996-2005) was 0 to 24,795 pounds, primarily for structural pest control (CDPR 2007, p.16). It is also used commercially in industrial water treatment and in rubber manufacture.

Potassium dimethyldithiocarbamate is listed under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, codified at Health and Safety Code section 25249.5 et seq.) as known to the State to cause reproductive toxicity (developmental toxicity endpoint), effective March 30, 1999. The Proposition 65 listing of potassium dimethyldithiocarbamate was based on a formal identification by the U.S. Environmental Protection Agency (U.S. EPA) of potassium dimethyldithiocarbamate as causing developmental toxicity (U.S. EPA, 1994a, b). U.S. EPA is an authoritative body under Proposition 65 for identification of chemicals as causing reproductive toxicity (Title 22, California Code of Regulations, section 12306(l))[1].

Procedures for the development of Proposition 65 MADLs are provided in regulation (Sections 12801 and 12803). Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As defined in regulations, a MADL is derived from a No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality (Section 12803(a)(4)).

[1] All further references to regulations are to Title 22 of the California Code of Regulations, unless otherwise noted

Study Selection

Relevant studies on the reproductive toxicity of potassium dimethyldithiocarbamate have been identified through literature searches. These studies have been reviewed and considered for the establishment of the MADL.

No human studies relevant to potassium dimethyldithiocarbamate reproductive toxicity were identified. Potassium dimethyldithiocarbamate has been tested for developmental toxicity in rats (Rodwell, 1988a) and rabbits (Rodwell, 1988b) as a registered pesticide. These are the only available studies of potassium dimethyldithiocarbamate reproductive toxicity. These studies were conducted under federal guidelines, met the requirements of Good Laboratory Practices, and were intended to provide information for health risk assessment. It is generally assumed in developmental toxicity risk assessment that "an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development [and]…the types of developmental effects seen in animal studies are not necessarily the same as those that may be produced in humans" (U.S. EPA, 1991). 50% potassium dimethyldithiocarbamate formulation was used in the developmental toxicology studies. The formulation is produced by solution phase synthesis and is stable under the resulting alkaline conditions (pH 11-14).

In the rat developmental toxicity study (Rodwell, 1988a), the 50% formulated potassium dimethyldithiocarbamate microbiocide was administered by gavage at doses of 0, 25, 150 or 400 mg/kg-day, corresponding to 12.5, 75 or 200 mg potassium dimethyldithiocarbamate /kg-day, to Sprague Dawley rats from gestation day 6 through 15. A lower fetal body weight in the high dose group than in controls (not statistically significant) was reported. The NOEL for this study was 75 mg potassium dimethyldithiocarbamate /kg-day.

The NOEL used for MADL development is based on the most sensitive study deemed to be of sufficient quality (Section 12803(a)(4)). The study that meets this criterion is Rodwell (1988b). In this rabbit developmental toxicity study, the 50% potassium dimethyldithiocarbamate microbiocide was administered by gavage at doses of 0, 25, 75 or 150 mg/kg-day, corresponding to 12.5, 37.5 or 75 mg potassium dimethyldithiocarbamate /kg-day, to New Zealand white rabbits on gestation days 6 through 18. At the high dose (75 mg potassium dimethyldithiocarbamate /kg-day), two does aborted and only 5 fetuses were available for evaluation. At the mid dose (37.5 mg potassium dimethyldithiocarbamate /kg-day), statistically significant fetal effects included a higher incidence of early resorptions, skeletal malformations and skeletal variations, and a smaller live litter size relative to controls. The NOEL from this study, 12.5 mg potassium dimethyldithiocarbamate /kg-day, served as the basis for calculation of the MADL.

Table 1. Studies on the developmental toxicity of potassium dimethyldithiocarbamate[1]

Study	Animals	Treatment	Maternal toxicity	Developmental toxicity
Rodwell, 1988a	Rats, S-D 28/group	Gavage, 0, 25, 150, 400 mg microbiocide[2] /kg-day [0, 12.5, 75, 200 mg potassium dimethyldithiocarbamate/ kg-day] gd 6-15	Clinical observations, Weight gain NOEL, 25 mg microbiocide[2]/kg-day [12.5 mg potassium dimethyldithio-carbamate/kg-day]	Fetal weight NOEL, 150 mg microbiocide[2] /kg-day [75 mg potassium dimethyldithiocarbamate/kg-day]
Rodwell, 1988b	rabbits, NZW 20/group	Gavage, 0, 25, 75, 150 mg microbiocide[2]/kg-day [0, 12.5, 37.5, 75 mg potassium dimethyldithiocarbamate/ kg-day] gd 6-18	Maternal death Weight gain LOEL, 25 mg microbiocide[2] /kg-day [12.5 mg potassium dimethyldithio-carbamate/kg-day]	Abortion Resorption Live litter size Skeletal malformation/variation NOEL, 25 mg microbiocide[2]/kg-day [12.5 mg potassium dimethyldithiocarbamate/kg-day]

[1]abbreviations: S-D= Sprague-Dawley, NZW=New Zealand White, gd=gestation day
[2] the microbiocide is a 50% formulation of potassium dimethyldithiocarbamate

Table 2. Dose-dependent developmental effects of potassium dimethyldithiocarbamate in rabbits

		Dose (mg KDDC/kg/d)			
Endpoint	0	0	25	75	150
Resorption/litter	0.6±0.7[1]	1.9±2.7	1.7±1.7	2.1±1.4**	3.8±2.9**
Live litter size	4.9±3.0	4.6±3.1	4.9±3.3	3.5±3.6**	0.5±1.1**
Fetal weight (g)	46.5±6.0	47.6±5.7	45.1±7.2	41.1±8.7	37.9±2.2
malformed fetus	0/16[2] (0)	3/14 (21)	0/15 (0)	5/11* (45)	1/2 *(50)*

[1] mean ± sd
[2] affected/total fetuses (percent)
* $p<0.05$, as reported by study authors
** $p<0.01$, as reported by study authors

MADL Calculation

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (Section 12803(a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Section 12803(b)). For oral and dermal routes of exposure, the following calculations were performed to derive the MADL for

potassium dimethyldithiocarbamate, based on a NOEL of 12.5 mg/kg-day for the oral route from the most sensitive study deemed to be of sufficient quality (Rodwell, 1988b). NOEL = 12.5 mg/kg-d

The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Section 12803(b)). For developmental toxicity, the assumed body weight of a pregnant woman is 58 kg.

12.5 mg/kg-day × 58 kg = 725 mg/day

The MADL is derived by dividing the NOEL by one thousand (1,000) to arrive at the maximum allowable dose level (§12801(b)(1)). Thus, the adjusted NOEL is divided by 1,000 to obtain the MADL:

MADL = 725 mg/day ÷ 1000 = 725 µg/day = **720 µg/day** after rounding.

Risk assessments for potassium dimethyldithiocarbamate use as a pesticide are usually based on the 50% pesticide formulation. For a pesticide formulation of 50% sodium dimethyldithiocarbamate, the **MADL** = 720 µg/day × 100 ÷ 50 = 1450 µg/day = **1400 µg/day** after rounding.

The MADL of 720 µg/day is applicable to exposure via oral, inhalation or dermal routes of exposure. If exposures occur by multiple (e.g. inhalation or dermal) routes, the total exposure to the chemical from a single source or product must be considered. If the total exposure resulting from any one or multiple routes is less than or equal to 72 µg/day, the MADL has not been exceeded.

References

California Department of Pesticide Regulation (CDPR 2007) Summary of Pesticide Use Report Data 2005 by Commodity. p.16. Available at http://cdpr.ca.gov.docs/pur.

Rodwell DE (1988a) Teratology study in rats with Busan85. SLS Study No 3138.17. Springborn Life Sciences, Inc., Wareham, MA. pp.1-19, 29.

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U.S. Environmental Protection Agency (U.S. EPA 1991) Guidelines for Developmental Toxicity Risk Assessment. Federal Register (56 FR 63798).

U.S. Environmental Protection Agency (U.S. EPA 1994a). Addition of Certain Chemicals; Toxic Chemical Release Reporting: Community Right to Know. Proposed Rule. Federal Register (59 FR 1788).

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